IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: **Garvey et al**

Application No: **10/024,040** Group Art Unit: **1614**

Filed: **December 21, 2001** Examiner: **R. Henley**

For: **Methods for Treating Female Sexual Dysfunctions Using S-Nitrosothiols**

Attorney Docket No: **102258.326 US2**

Commissioner of Patents
PO Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C. F. R. § 1.131

I, David S. Garvey, Ph.D. declare the following:

1. I am currently the Executive Project Director and Chief Chemistry Advisor at NitroMed, Inc. (NitroMed). From 1997 to 2003, I was the Senior Director of Chemistry at NitroMed. From 1994 to 1997, I was the Director of Chemistry at NitroMed.

2. I am a co-inventor of U.S. Application No. 10/024,040, filed December 21, 2001 (hereafter "the present application").

3. I have reviewed and am familiar with the specification and claims of the present application; the Office Action dated July 24, 2003, for the present application; and the references cited by the Examiner in the Office Action dated July 24, 2003, for the present application.

4. Attached hereto as Exhibit A is a document entitled "NitroMed Memorandum" dated October 29, 1997, from me to Charles Herron (NitroMed's patent attorney at Carella, Byrne, Bain, Gilfillan, Cecchi, Stewart & Olstein) regarding "NO-PDE Inhibitor PCT." The first paragraph of the memorandum states:

> Enclosed are floppy disk and paper copies of the updated version of this application. ...I think you will find it is suitable for filing as is.

5. To the best of my knowledge, recollection and belief, the floppy disk and paper copies of the application identified in the memorandum dated October 29, 1997, were the same as the application that was ultimately filed on October 31, 1997, as PCT/US97/19870, to which the present application claims priority. The specification of the present application is the same as the specification of PCT/US97/19870.

6. To the best of my knowledge, recollection and belief, the application identified in the memorandum dated October 29, 1997, was prepared prior to October 28, 1997.

7. To the best of my knowledge, recollection and belief, prior to October 28, 1997, the draft application contained the same or substantially the same information as the application identified in the memorandum dated October 29, 1997, and the application filed October 31, 1997, as PCT/US97/19870.

8. To the best of my knowledge, recollection and belief, prior to October 28, 1997, the draft application contained, *inter alia*, information that described methods of treating female sexual dysfunction by administering a pharmaceutical formulation comprising an S-nitrosothiol.

9. To the best of my knowledge, recollection and belief, I did not save any drafts of the application that was ultimately filed on October 31, 1997, as PCT/US97/19870 because it was NitroMed's policy not to save any draft patent applications.

10. I have worked with S. William Tam, Ph.D. (Dr. Tam) at NitroMed since 1994, and we generally have conversations about the research NitroMed is conducting in the chemical and biological areas and the subject matter in the patent applications that NitroMed is filing.

11. Prior to October 28, 1997, I had conversations with Dr. Tam about the disclosure in the draft application that was ultimately filed as PCT/US97/19870. In particular, I verbally conveyed to Dr. Tam that the application described methods for treating female sexual dysfunctions using S-nitrosothiols.

12. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements so made are punishable by fine or imprisonment or both, under § 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity or enforceability of this application or any patent issued thereon.

David S. Garvey, Ph.D.

1/23/04
Date

NitroMed Memorandum

DATE: October 29, 1997

TO: *Charles Herron*

FROM: *Dave Garvey*

RE: *NO-PDE Inhibitor PCT*

Charlie,

Enclosed are floppy disk and paper copies of the updated version of this application. The file copy is in MS Word for Windows (PAPDE.doc) as well as Word (PAPDE2.doc) and you should be able to do any additional editing without any problems, however, I think you will find it is suitable for filing as is.

I'll give you a call mid day Thursday to make sure you have received the package and to answer any questions you have.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: **Garvey et al**

Application No: **10/024,040** Group Art Unit: **1614**

Filed: **December 21, 2001** Examiner: **R. Henley**

For: **Methods for Treating Female Sexual Dysfunctions Using S-Nitrosothiols**

Attorney Docket No: **102258.326 US2**

Commissioner of Patents
PO Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C. F. R. § 1.131

I, S. William Tam, Ph.D. declare the following:

1. I am currently the Senior Director of Clinical Program Development at NitroMed, Inc. (NitroMed). I was the Senior Director of Clinical Development and Project Management at NitroMed from 2001 to 2002. From 1997 to 2001, I was the Senior Director of Biology at NitroMed, and from 1994 to 1997 I was the Director of Pharmacology at NitroMed.

2. I have worked with David S. Garvey, Ph.D. (Dr. Garvey) at NitroMed since 1994, and we generally have conversations about the research NitroMed is conducting in the chemical and biological areas and the subject matter in the patent applications that NitroMed is filing.

3. Prior to October 28, 1997, I had conversations with Dr. Garvey about the disclosure in the draft application that was ultimately filed as PCT/US97/19870. In particular, Dr. Garvey verbally conveyed to me that the application described methods for treating female sexual dysfunctions using S-nitrosothiols.

4. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements so made are punishable by fine or imprisonment or both, under § 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity or enforceability of this application or any patent issued thereon.

S. William Tam, Ph.D.

1/23/2004
Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: **Garvey et al**

Serial No.: **10/024,550**

Filing Date: **December 21, 2001**

Publication No. **2002/0061879**

Title: **Nitrosated and Nitrosylated Alpha-Adrenergic Receptor Antagonist Compounds, Compositions and Their Uses**

PENDING CLAIMS

35. (New) A method of treatment, in an organism, of a vascular condition, comprising administration of at least one agent at a level which enhances NO and which does not appreciably alter normal systemic vascular tone in said organism.

36. (New) A method for treating sexual dysfunction in a female individual, comprising administering to the vagina, vulvar area and/or urethra of the individual a pharmaceutical formulation that comprises an effective amount of a nitrovasodilator selected from the group consisting of sodium nitroprusside, diazenium diolates, molsidomine, linsidomine chlorohydrate, S-nitrosothiols, organic nitrates, pharmacologically acceptable salts, esters, analogs, derivatives, prodrugs and inclusion complexes of any of the foregoing, and combinations thereof.

37. (New) A method of enhancing sexuality in a female having a clitoris comprising the step of topically administering to a surface of the clitoris a composition whose primary agent is a vasodilator and whose secondary agent is a carrier in which the vasodilator is dispersed to deliver it directly to said surface so that it is retained and absorbed thereby, said composition being in a formulation and in a dosage which is substantially free of toxicity and therefore does not give rise to an adverse reaction.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: **Garvey et al**

Application No: **09/478,222** Group Art Unit: **1627**

Filed: **January 5, 2000** Examiner: **B. Celsa**

For: **Methods for Treating Human Impotence with Nitric Oxide Donor Compounds**

Attorney Docket No: **102258.346**

Pending Claims

61. (Original) A method for treating female impotence in a female individual in need thereof comprising administering to the female individual a therapeutically effective amount of a composition comprising an S-nitrosothiol compound and a pharmaceutically acceptable carrier.

63. (Original) The method of claim 61, wherein the S-nitrosothiol compound is S-nitroso-N-acetylcysteine, S-nitroso-captopril, S-nitroso-homocysteine, S-nitroso-cysteine or S-nitroso-glutathione.

64. (Original) The method of claim 63, wherein the S-nitrosothiol compound is S-nitroso-glutathione.

65. (Previously Amended) The method of claim 61, wherein the S-nitrosothiol compound is

(i) $CH_3(C(R_e)(R_f))_xSNO$;

(ii) $HS(C(R_e)(R_f))_xSNO$;

(iii) $ONS(C(R_e)(R_f))_xB$; or

(iv) $H_2N\text{-}CH(CO_2H)\text{-}(CH_2)_x\text{-}C(O)NH\text{-}CH(CH_2SNO)\text{-}C(O)NH\text{-}CH_2\text{-}CO_2H$;

wherein x is 2 to 20; R_e and R_f are each independently hydrogen, lower alkyl, cycloalkyl, aryl, heteroaryl, arylalkyl, amino, alkylamino, amido, alkylamido, dialkylamino, or carboxy; or R_e and R_f taken together with the carbon atom to which they are attached are carbonyl, cycloalkyl or bridged cycloalkyl; and B is fluoro, C_1-C_6 alkoxy, cyano, carboxamido, cycloalkyl, arylalkoxy, alkylsulfinyl, arylthio, alkylamino, dialkylamino, hydroxy, carbamoyl, N-alkylcarbamoyl, N,N-dialkylcarbamoyl, amino, hydroxyl, carboxyl, hydrogen, nitro or aryl.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:	**Marek et al**
Application No.:	**09/850,081**
Filed:	**May 8, 2001**
Group Art Unit:	**1617**
Examiner:	**L. Wells**
For:	**COMPOSITIONS OF S-NITROSOTHIOLS AND METHODS OF TREATING SEXUAL DYSFUNCTIONS**
Publication No.	**2001/0046471**

Allowed Claims

100. A method for treating a female sexual dysfunction in a patient in need thereof comprising topically administering to the vagina or vulvar area of the patient a therapeutically effective amount of a composition comprising at least one S-nitrosothiol compound or a pharmaceutically acceptable salt thereof; at least one glyceride; and a pharmaceutically acceptable carrier.

101. The method of claim 100, wherein the S-nitrosothiol compound is S-nitroso-N-acetylcysteine, S-nitroso-captopril, S-nitroso-N-acetylpenicillamine, S-nitroso-homocysteine, S-nitroso-cysteine, S-nitroso-glutathione or S-nitroso-cysteinyl-glycine.

102. The method of claim 101, wherein the S-nitrosothiol compound is S-nitroso-glutathione.

103. The method of claim 100, wherein the S-nitrosothiol compound is:

(i) $HS(C(R_e)(R_f))_mSNO$;

(ii) $ONS(C(R_e)(R_f))_mR_e$; or

(iii) $H_2N\text{-}CH(CO_2H)\text{-}(CH_2)_m\text{-}C(O)NH\text{-}CH(CH_2SNO)\text{-}C(O)NH\text{-}CH_2\text{-}CO_2H$;

wherein m is an integer from 2 to 20; R_e and R_f are each independently a hydrogen, an alkyl, a cycloalkoxy, a halogen, a hydroxy, an hydroxyalkyl, an alkoxyalkyl, an arylheterocyclic ring, an alkylaryl, a cycloalkylalkyl, a heterocyclicalkyl, an alkoxy, a haloalkoxy, an amino, an alkylamino, a dialkylamino, an arylamino, a diarylamino, an alkylarylamino, an alkoxyhaloalkyl, a haloalkoxy, a sulfonic acid, a sulfonic ester, an alkylsulfonic acid, an arylsulfonic acid, an arylalkoxy, an alkylthio, an arylthio, a cycloalkylthio, a cycloalkenyl, a cyano, an aminoalkyl, an aminoaryl, an aryl, an arylalkyl, an alkylaryl, a carboxamido, a alkylcarboxamido, an arylcarboxamido, an amidyl, a carboxyl, a carbamoyl, a carbamate, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarbonyl, an arylcarbonyl, an ester, a carboxylic ester, an alkylcarboxylic ester, an arylcarboxylic ester, a haloalkoxy, a sulfonamido, an alkylsulfonamido, an arylsulfonamido, a sulfonic ester, a urea, a phosphoryl, a nitro, -T-Q , or $-(C(R_e)(R_f))_k$-T-Q, or R_e and R_f taken together with the carbons to which they are attached form a carbonyl, a methanthial, a heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group; Q is -NO or $-NO_2$; and T is independently a covalent bond, a carbonyl, an oxygen, $-S(O)_o$- or $-N(R_a)R_i$-,

wherein o is an integer from 0 to 2, R_a is a lone pair of electrons, a hydrogen or an alkyl group; R_i is a hydrogen, an alkyl, an aryl, an alkylcarboxylic acid, an aryl carboxylic acid, an alkylcarboxylic ester, an arylcarboxylic ester, an alkylcarboxamido, an arylcarboxamido, an alkylaryl, an alkylsulfinyl, an alkylsulfonyl, an arylsulfinyl, an arylsulfonyl, a sulfonamido, a carboxamido, a carboxylic ester, an amino alkyl, an amino aryl,-CH_2-C(T-Q)(R_e)(R_f), or -(N_2O_2-)•M^+, wherein M^+ is an organic or inorganic cation; with the proviso that when R_i is -CH_2-C(T-Q)(R_e)(R_f) or -(N_2O_2-)•M^+; then "-T-Q" can be a hydrogen, an alkyl group, an alkoxyalkyl group, an aminoalkyl group, a hydroxy group or an aryl group.

104. The method of claim 100, wherein the glyceride is a mono glyceride, a diglyceride, a triglyceride, a polyglycolyzed glyceride, or a mixture thereof.

105. The method of claim 100, wherein the glyceride is a mixture of caprylic triglycerides and capric triglycerides, a decanoly triglyceride, an octanoyl triglyceride, a C_8-C_{12} triglyceride, a saturated polyglycolyzed glyceride, a glyceryl caprylate/caprate and PEG-8 (polyethylene glycol) caprylate/caprate complex, a unsaturated polyglycolyzed glyceride, an apricot kernel oil PEG-6 complex, an almond oil PEG-6 complex, a peanut oil PEG-6 complex, an olive oil PEG-6 complex, a corn oil PEG-6 complex, an ethoxylated glyceride, a glyceryl caprylate/caprate PEG-4 complex, or a mixture thereof.

106. The method of claim 100, wherein the composition is in the form of a cream, a spray, a lotion, a gel, an ointment, an emulsion, a foam, a coating for a condom, or a liposome composition.

107. The method of claim 100, further comprising administering to the patient a therapeutically effective amount of at least one vasoactive agent.

108. The method of claim 107, wherein the vasoactive agent is a potassium channel activator, a calcium channel blocker, an α-adrenergic receptor antagonist, a β-blocker, a phosphodiesterase inhibitor, adenosine, an ergot alkaloid, a vasoactive intestinal peptide, a prostaglandin, a dopamine agonist, an opioid antagonist, an endothelin antagonist, a thromboxane inhibitor or a mixture thereof.

109. The method of claim 100, further comprising administering to the patient at least one compound that donates, transfers or releases nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase.

110. The method of claim 109, wherein the at least one compound that donates, transfers or releases nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase is:

(i) a compound that comprises at least one ON-O-, ON-N- or ON-C- group;

(ii) a compound that comprises at least one O_2N-O-, O_2N-N-, O_2N-S- or O_2N-C- group;

(iii) a N-oxo-N-nitrosoamine having the formula: R^1R^2-N(O-M^+)-NO, wherein R^1 and R^2 are each independently a polypeptide, an amino acid, a sugar, an oligonucleotide, a straight or

branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted hydrocarbon, or a heterocyclic group, and M^+ is an organic or inorganic cation.

111. The method of claim 110, wherein the compound comprising at least one ON-O-, ON-N- or ON-C- group is an ON-O-polypeptide, an ON-N-polypepetide, an ON-C-polypeptide, an ON-O-amino acid, an ON-N-amino acid, an ON-C-amino acid, an ON-O-sugar, an ON-N-sugar, an ON-C-sugar, an ON-O-oligonucleotide, an ON-N-oligonucleotide, an ON-C-oligonucleotide, a straight or branched, saturated or unsaturated, substituted or unsubstituted, aliphatic or aromatic ON-O-hydrocarbon, a straight or branched, saturated or unsaturated, substituted or unsubstituted, aliphatic or aromatic ON-N-hydrocarbon, a straight or branched, saturated or unsaturated, substituted or unsubstituted, aliphatic or aromatic ON-C-hydrocarbon, an ON-O-heterocyclic compound, an ON-N-heterocyclic compound or a ON-C-heterocyclic compound.

112. The method of claim 110, wherein compound comprising at least one O_2N-O-, O_2N-N-, O_2N-S- or O_2N-C- group is an O_2N-O-polypeptide, an O_2N-N-polypeptide, an O_2N-S-polypeptide, an O_2N-C-polypeptide, an O_2N-O-amino acid, O_2N-N-amino acid, O_2N-S-amino acid, an O_2N-C-amino acid, an O_2N-O-sugar, an O_2N-N-sugar, O_2N-S-sugar, an O_2N-C-sugar, an O_2N-O-oligonucleotide, an O_2N-N-oligonucleotide, an O_2N-S-oligonucleotide, an O_2N-C-oligonucleotide, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O_2N-O-hydrocarbon, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O_2N-N-hydrocarbon, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O_2N-S-hydrocarbon, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O_2N-C-hydrocarbon, an O_2N-O-heterocyclic compound, an O_2N-N-heterocyclic compound, an O_2N-S-heterocyclic compound or an O_2N-C-heterocyclic compound.

113. The method of claim 109, wherein the at least one compound that donates, transfers or releases nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase is L-arginine, L-homoarginine, N-hydroxy-L-arginine, nitrosated L-arginine, nitrosylated L-arginine, nitrosated N-hydroxy-L-arginine, nitrosylated N-hydroxy-L-arginine, citrulline, ornithine, glutamine, lysine, a polypeptide comprising at least one of these amino acids or an inhibitor of the enzyme arginase.

114. The method of claim 109, wherein the at least one compound that donates, transfers or releases nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase is a NONOate.